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Peritoneal Mesothelioma: Clinical and Therapeutic Aspects

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Abstract

Mesothelioma is a very rare malignant disease that originates from mesothelial cells that line the serosa: pleura, peritoneum, pericardium, or testicular vaginal tunic. Peritoneal mesothelioma accounts for 7–10% of all mesotheliomas diagnosed, and ranks second after pleural localization of mesothelioma. The incidence of peritoneal mesothelioma is 0.5–3 cases per million in men and 0.2–2 cases per million in women. Diagnosis of peritoneal mesothelioma is difficult due to non-specific symptoms and because of this patients present in advanced stages of the disease. Histologically there are three major categories of malignant peritoneal mesothelioma: epithelioid, sarcomatoid, and biphasic. The differential diagnosis of peritoneal mesothelioma is made with peritoneal pseudomyxoma, ovarian tumors, and peritoneal metastases from colorectal cancer. An important role in differential diagnosis, in addition to immunohistochemistry, is played by various tumor markers and genetic tests. The treatment of peritoneal mesothelioma is performed by cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), with good results for patients in the early stages of the disease. For patients with advanced disease, a new treatment has been proposed: pressurized intraperitoneal aerosol chemotherapy (PIPAC). For patients who cannot use CRS and HIPEC, the only therapeutic option remains chemotherapy (systemic + intraperitoneal).

Keywords: peritoneal mesothelioma, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy

1. Introduction

Mesotheliomas arise from cells lining the serosa: pleural, pericardial, peritoneal, and testicular vaginal tunic. Mesothelial tumors range from localized malignant mesothelioma to aggressive diffuse malignancies that invade the anatomical structures of the neighborhood and can give distant metastases. Rare mesothelial tumors that represent less than 1% of all diagnosed mesothelial tumors are paratesticular mesothelioma and pericardial mesothelioma. The peritoneal localization of mesothelioma is on the second place after the pleural localization. Peritoneal mesothelioma (PM) is a rare disease with an incidence of 0.6–3 per million in men and 0.2–2 per million in women [1]. Diffuse malignant

peritoneal mesothelioma (DMPM), which accounts for 30% of all malignant mesotheliomas, is characterized by symptomatic polymorphism and difficulty in establishing a positive diagnosis. In this sense, the immunohistochemical examination has a very important role in differentiating this disease from peritoneal carcinomatosis [2].

2. Peritoneal mesothelioma: Symptomatology, histopathology, differential diagnosis, and treatment

2.1 Symptomatology of PM

The vast majority of patients are asymptomatic. The most common signs appear when the tumor mass compresses the neighboring organs or the rupture of cystic tumor formations mimicking the symptoms of acute peritonitis, as happened in the case operated and treated in our surgery clinic. Thus, the most common symptoms are abdominal pain, ascites, anorexia, weight loss, palpable tumor formation, and localized or generalized muscle defense [3].

Due to the more frequent localization of peritoneal mesothelioma on the pelvic peritoneum, peritoneal adhesions appear on the rectum, uterus, and bladder, causing the appearance of other symptoms such as dysuria, urinary symptoms, intestinal obstruction, and dyspareunia.

Peritoneal mesothelioma should be differentiated from multicystic peritoneal mesothelioma (MCPM) which is a benign, multicystic abdominal tumor such as cystic lymphangioma, endometriosis, cystic adenomatoid tumor, pseudomyxoma peritonei, and malignant peritoneal mesothelioma. For the positive diagnosis of MCPM, it is necessary to perform an immunohistochemical examination [3].

Benign multicystic peritoneal mesothelioma (BMPM) known as multilocular peritoneal cysts is an extremely rare disease which has the peritoneal mesothelium as a starting point. Although this disease is considered benign, relapse after surgery is reported in over 50% of cases [4] and two cases of malignant transformation have been reported [5]. Pathogenesis of the disease is unknown. There is a discussion of a possible etiopathogenicity related to pelvic inflammatory disease, Mediterranean fever, endometriosis, and a history of abdominal surgery. Three hypotheses have been proposed in the etiology of BMPM disease. One hypothesis argues that BMPM arises from an inflammatory process involving peritoneum, which results in hyperplastic and dysplastic reactive transformation of peritoneal mesothelial cells. Another theory supports the primary neoplastic origin without the involvement of a chronic inflammatory process. Other authors support the hormonal theory in which the development and progression of BMPM is closely related to sensitivity to sexual hormones. This theory is supported by the fact that BMPM has a higher incidence in women during the reproductive period and that BMPM responds to tamoxifen and gonadotropin-releasing hormone analogs [6]. Most authors agree on the fact that chronic peritoneal inflammatory process causes proliferation and migration of peripheral mesothelial cells often associated with metaplasia of the underlying connective tissue [6–8]. Transition between multicystic mesothelioma and adenomatoid tumor has been observed on several occasions [9, 10].

The symptoms of BMPM are insignificant but become apparent when the cystic tumors are large enough to produce mass effect on surrounding organs, or if the cysts break and produce an acute peritonitis-like reaction, as we have shown. Symptoms may be chronic abdominal and/or pelvic pain, abdominal distension, intestinal obstruction, and intestinal transit disorders [1, 11–13].

The physical examination may reveal muscle defense, abdominal distension, or acute appendicitis-like symptoms [14].

There are benign or malignant diseases that can mime BMPM. These diseases are intestinal lymphangioma and malignant peritoneal mesothelioma. Lymphangioma can be diagnosed when the cysts contain predominantly chylous fluid [15] and when the presence of lymphoid aggregates, smooth muscle cells, and D2-40-positive immunoexpression is discovered in the immunohistochemical examination. Malignant peritoneal mesothelioma has a history of asbestos exposure, abdominal pain, and weight loss.

2.2 Histopathology of PM

Three histological types of peritoneal mesothelioma have been described: epithelioid, sarcomatoid, and biphasic. Patients with sarcomatoid and biphasic subtypes have a more reserved prognosis than patients with the epithelioid subtype. Multicystic mesothelioma and well-differentiated papillary mesothelioma are forms of peritoneal mesothelioma that have a favorable prognosis.

2.2.1 Benign mesothelioma

Benign mesothelioma is a term applied to solitary lesions of peritoneum. Two types of benign mesothelial proliferation in the peritoneal cavity are benign multicystic peritoneal mesothelioma (MCPM) and adenomatoid tumor.

2.2.2 Malignant mesothelioma

Malignant mesothelioma is commonly found in adults and serum levels of osteopontin and mesothelin are serum biomarkers used for diagnosis.

Well-differentiated papillary mesothelioma of peritoneum is multicentric, extensive, and is characterized by prominent formation of papillae lined by bland mesothelial cells with minimal or no invasion. These are associated with an evolution without clinical symptoms, and people with this clinical form of mesothelioma have a long survival.

Deciduoid mesothelioma is characterized by the presence of large tumor cells with an abundant ground-glass cytoplasm that simulates the appearance of decidual cells. This histological form has been described in young women, located not only in the pelviperitoneal cavity but also in the pleural cavity in patients of both sexes. It is characterized by a short survival.

Mesothelioma with clear cell features can be confused with metastatic carcinoma from the kidney. The cytoplasmic clearing is due to the accumulation of glycogen in which case the alternative term glycogen-rich mesothelioma has been used.

Malignant mesothelioma with small cell is characterized by the presence of small cells. Most of reported cases have been immunoreactive for keratin and mesothelial markers including calretinin, CK 5/6, WT1, and podoplanin; some cases also stained for neuron-specific enolase and occasionally CD 57.

Lymphohistiocytoid mesothelioma is characterized microscopically by a diffuse proliferation of atypical histiocyte-like malignant mesothelial cells admixed with numerous lymphocytes (T-cell type) and lesser number of plasma cells. The phenotype of the histiocyte-like elements reflects their mesothelial nature and the behavior of this tumor is aggressive.

Pleomorphic mesothelioma in the WHO classification scheme is considered a variant of epithelioid mesothelioma and is characterized by pleomorphic large cells with abundant eosinophilic cytoplasm and single or multiple nuclei with

marked variation in size and large nucleoli. The staining for traditional markers of mesothelioma-like calretinin, CK 5/6, and WT1 is variable but they are intense positive for pankeratin and cytokeratin 7. These tumors are a variant of sarcomatous tumors rather than epithelioid mesothelioma, being characterized by an aggressive behavior characteristic of sarcomatous tumors.

Desmoplastic mesothelioma is a subtype of sarcomatoid epithelioma, characterized by abundant deposition of fibrous tissue demonstrating a storiform arrangement of neoplastic spindle cells. The main differential diagnosis is with benign fibrous proliferations. Immunohistochemical receptors for keratin, calretinin, and WT1 is in favor of desmoplastic mesothelioma.

2.3 Role of immunohistochemistry, electron microscopy, and molecular testing in differential diagnosis of mesothelioma

2.3.1 Immunohistochemistry and electron microscopy

The diagnosis of malignant mesothelioma in the absence of detectable invasion is problematic in the absence of invasive disease. Homozygous deletion of p16^{INK4a} (CDKN2A) detected using a fluorescent in situ hybridization (FISH) assay and loss of BAP1 expression by immunohistochemistry may be helpful in separating benign from malignant mesothelial proliferations including desmoplastic mesothelioma.

Other immunostains such as epithelial membrane antigen (EMA), p53, GLUT1, and IMP3 are proposed for separating benign from malignant mesothelial proliferations. Malignant epithelioid mesotheliomas need to be distinguished from metastatic carcinoma, specially adenocarcinomas with pseudo-mesotheliomatous growth pattern [3, 16].

The role of immunohistochemistry is in separating sarcomatoid mesotheliomas from sarcomatoid carcinomas and soft tissue sarcomas [2]. Mesotheliomas usually produce large amounts of hyaluronic acid, which can be demonstrated with the alcian blue or colloidal iron stains. The presence of obvious droplets of mucicarmine-positive or periodic acid-Schiff (PAS)-positive material in the cytoplasm of the tumor cell makes the diagnosis of mesothelioma very unlikely, although it does not rule it out completely inasmuch as the existence of rare mucin-positive mesotheliomas has been demonstrated.

Electron microscopy played an important role in the differential diagnosis between mesothelioma and metastatic carcinoma. This was primarily based on the appearance of the microvilli in the apical surface of the tumor cells, which in mesothelioma are longer and more slender than those in adenocarcinoma.

Many metastatic adenocarcinomas likely to be confused with mesothelioma are positive for cytokeratin 7, as are epithelioid mesotheliomas, making cytokeratin 7, as are epithelioid mesotheliomas, making cytokeratin 7 and 20 of limited value except in very specific context of metastases from the gastrointestinal tract.

The following immunostains are most commonly available and utilized in differential diagnosis of mesothelioma:

1. Epithelial markers that are usually present in both tumors (mesothelioma and metastatic carcinoma): pankeratins, EMA, and basement membrane components;
2. Organ-associated and lineage-specific markers that are often expressed in metastatic carcinoma but not mesothelioma: napsin A (lung and kidney), PAX8 (kidney, mullerian, thymus), CDX2 (gastrointestinal tract, pancreatobiliary),

p63/p40 (squamous cell, urothelial), and GATA3 (breast, urothelial, squamous cell);

3. Markers that are usually expressed in metastatic carcinoma but not mesothelioma: MOC-31, Ber-EP4, carcinoembryonic antigen (CEA), B72.3, BG8, CD15, MUC4, and claudin-4;
4. Markers that are usually expressed in mesothelioma but not in carcinoma: calretinin (breast, mullerian serous), WT1 (breast, mullerian serous), keratin 5/6 (urothelial, squamous cell), D2-40/podoplanin (mullerian serous, squamous cell), and thrombomodulin (squamous cell).

2.3.2 Molecular genetic features

Mutations in the TP 53 gene are uncommon. In 60–80% of mesothelioma cases, homozygous deletion of p16^{INK4a} (CDKN2A) is found, which is an investigation used to differentiate benign mesothelial disorders from malignant mesothelial proliferations. CDKN2A deletion is a potential biomarker for a more aggressive course in some cases of mesothelioma. The most common recurrent somatic mutations in malignant mesothelioma target three genes functioning as tumor suppressors: cyclin-dependent kinase inhibitor 2A (CDKN2A), BCRA1-associated protein 1 (BAP1), and neurofibromin 2 (merlin) (NF2).

2.3.3 Differential radiological and histopathological diagnosis

Differential diagnosis is made with other peritoneal malignancies such as peritoneal pseudomyxoma, ovarian tumors, and peritoneal metastases from colorectal cancer. Peritoneal pseudomyxoma is a rare disease characterized by multifocal epithelial deposits in the peritoneal cavity, secreted by mucin, with or without gelatinous ascites, in the absence of extraperitoneal involvement [17]. It was first described by Werth and later by Rokitsky in 1942, being considered a fatal condition, with unexplained etiology. It predominates in women, the ovarian tumor pathology being incriminated as responsible in a significant percentage in the etiopathogenesis of peritoneal pseudomyxoma. In men, adenoma (mucocele) appendicular tumors and appendicular adenocarcinoma are the main cause described [17]. Virtually any primary solid tumor is the epicenter of the malignancy. In the case of peritoneal pseudomixoma, the predominant tumor volume is in the peritoneum, and the primary tumor is insignificant, whether it is appendicular, ovarian, or in other organs [18]. Pseudomyxoma peritonei involves the presence of mucinous, gelatinous deposits in the peritoneum, deposits that can reach impressive sizes. Thus, death can be caused by respiratory failure. It seems that the basis of this condition is a certain type of mucous cells that have a special pattern—the presence of MUC2 [18]. Removal of the tumor and gelatinous material is the purpose of treatment.

Peritoneal pseudomixoma is the most serious complication of the appendicular mucocele and develops as a result of spontaneous or iatrogenic implantation of the tumor into the peritoneal cavity [19]. The peritoneal and occasionally pleural pseudomixoma, which appeared as a result of the evolution of the appendicular mucocele, is rare and constitutes 6–8.8% [19–21]. Pseudomucinous cysts of the ovary, usually associated with appendicular mucocele, are the predominant cause of peritoneal pseudomixoma in older women and in men; the origin of peritoneal pseudomixoma is usually the vermiform appendix [21]. The pathology has a slow

evolution through the loss of intestinal function, fistula formation, and eventual death. The most common complications are occlusion and intestinal bleeding.

Extra-abdominal eruption of appendicular cystadenocarcinoma with spontaneous cutaneous fistula formation is extremely rare, being published only four cases in the world literature [22–25]. The pathogenetic mechanism of spontaneous skin fistula formation in patients with mucinous cystadenocarcinoma of the appendix is enigmatic, but we assume that the occurrence of this complication depends on the malignant nature of the tumor.

Patients with appendicular mucocele are asymptomatic in about 25% of cases; even in the case of large lesions, the most common complaints are pain in the right iliac fossa, similar to acute appendicitis and palpable tumor formation in 50% of cases [20, 21].

2.4 Treatment

Malignant peritoneal mesothelioma (MPM) is a rare disease with a recurrence rate of 40–50% after surgical debulking. Identifying the histological type of peritoneal mesothelioma, the number of invaded lymph nodes, and the Ki-67 proliferation marker are very important parameters for surgical treatment, but this is possible in most cases after laparotomy and cytoreductive surgery (CRS). The preoperative CT scan, performed by an experienced radiologist, can help us identify anatomical sites unfavorable for surgical treatment such as intestinal serosa and/or porta hepatis [26].

2.4.1 Cytoreductive surgery (CRS)

For the selection of patients benefiting from CRS, the peritoneal cancer index (PCI) is used, which consists of combining a score [27] given by 13 abdomino-pelvic regions (central, right upper, epigastrium, upper left, left flank, left lower, pelvis, right lower, right flank, upper jejunum, lower jejunum, upper ileum, lower ileum) to which lesion size score is added (LS 0—no tumor seen; LS 1—tumor up to 0.5 cm; LS 2—tumor up to 5 cm, and LS 3—tumor >5 cm or confluence).

In MPM, there is an intraoperative extensive invasion at the level of the parietal and visceral peritoneum on the surface of the small and large intestines but also in the mesentery and mesocolon. Lymph nodes will be removed whenever there is a suspicion of invasion, but a complete CRS may require resections of the small and large intestines (especially the splenic angle of the colon or the sigmoid colon). In order to achieve HIPEC, a complete hemostasis is needed; otherwise, intra-peritoneal hemorrhage occurs during the procedure. Before HIPEC, an extensive intraoperative peritoneal toilet will be performed either with distilled water or with diluted hydrogen peroxide (0.25%) or povidone iodine, which aim at the mechanical cleansing of possible cancer cells.

Recently, the use of cytoreductive surgery (CRS) in the treatment of peritoneal mesothelioma with hyperthermic intraperitoneal chemotherapy (HIPEC) has been discussed [28]. Median overall survival for patients with peritoneal mesothelioma treated by CRS and HIPEC ranges from 29 to 95 months [29–32].

Research [29] on 405 patients with peritoneal mesothelioma from 29 centers in Europe and the US reported that after treatment of peritoneal mesothelioma with CRS and HIPEC, a median survival of 53 months and 5-year overall survival rate of 47%. Overall survival of patients with peritoneal mesothelioma treated with chemotherapy alone (pemetrexed + cisplatin) was poor (approximately 13 months).

A study [33] of 1514 patients with peritoneal mesothelioma who were treated with CRS, CRS and HIPEC, and chemotherapy alone showed a survival

of 52 months for CRS, 61 months for CRS and HIPEC, and 17 months after chemotherapy.

The reduction of the MPM recurrence rate was obtained by combining CRS with HIPEC. The study conducted by Nizri and colleagues [34] on 19 patients with MPM who underwent CRS combined with HIPEC showed that after a median follow-up of 69 months, all patients were alive and only 4 of the 19 patients had recurrences (21%).

2.4.2 Hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), and normothermic intraperitoneal chemotherapy (NIPEC) in treatment of MPM

Additional chemotherapy was used to treat patients with MPM according to three therapeutic protocols as follows:

1. HIPEC with doxorubicin and cisplatin
2. Early postoperative intraperitoneal chemotherapy (EPIC) with paclitaxel that was added intraperitoneally in the first 5 days after CRS.
3. HIPEC then EPIC and then long-term intraperitoneal paclitaxel or pemetrexed intraperitoneally to which cisplatin is added intravenously as an adjunct to normothermic intraperitoneal chemotherapy (NIPEC).

In the absence of CRS and HIPEC, the median survival of patients with MPM is approximately 1 year. Aggressively applied surgical treatment along with additional chemotherapy increased the median survival of patients with MPM over 5 years.

The standard recommendations for HIPEC are cisplatin if renal function is good (250 mg/m^2), cisplatin plus doxorubicin, cisplatin plus mitomycin, or mitomycin only. There are also authors who use bidirectional chemotherapy by adding systemic ifosfamide plus mesna disulfide by continuing the 90-minute infusion of HIPEC with doxorubicin and cisplatin.

Survival in patients with MPM is improved in patients who used CRS plus HIPEC compared to patients who used CRS plus hyperthermic perioperative chemotherapy.

Recent studies [35] suggest a new therapeutic modality for patients with peritoneal mesothelioma: pressurized intraperitoneal aerosol chemotherapy (PIPAC). This new therapeutic modality, combined with systemic chemotherapy, may be an option for patients to whom CRS and HIPEC cannot be applied.

A retrospective study [36] of 29 patients with peritoneal mesothelioma treated with PIPAC (doxorubicin + cisplatin) showed encouraging results. Many patients with advanced peritoneal mesothelioma do not benefit from CRS and HIPEC, where chemotherapy (systemic + intraperitoneal) remains the only therapeutic option.

2.4.3 Molecular therapy and immunotherapy

One hope for molecular therapy in patients with MPM was the identification of ALK rearrangements that would be present in 3% of patients with MPM. This has been shown to be present in patients <40 years of age who have not been exposed to asbestos fibers. It is hoped that these patients will benefit from ALK inhibitors.

Gefitinib and erlotinib, which are tyrosine kinase inhibitors, acting on the epidermal growth factor receptor (EGFR), have been shown to have no significant action in MPM. By contrast, angiokinase inhibitors (nintedanib) acting on VEGF receptors, platelet-derived-growth factors, fibroblastic growth factors, and Src and Abl kinase signaling improved progression-free survival in patients with MPM when co-administered with pemetrexed and cisplatin [37].

Bevacizumab, which is an anti-VEGF antibody [38] in combination with cisplatin and pemetrexed, significantly increased overall survival in patients with MPM. Immune checkpoint inhibitors such as anti-CTLA 4 (tremelimumab and ipilimumab) and anti-PD1 antibodies (avelumab and durvalumab) are under investigation.

2.4.4 Recommendations in the treatment of MPM

The recommendations discussed at the Washington DC 2016 meeting by the Peritoneal Surface Oncology Group International (PSOGI) regarding therapeutic strategies [39] in patients with MPM were the following:

1. Patients with MPM who are operable will be given CRS and HIPEC. The applied surgical treatment will include peritonectomy procedures (there are still controversies related to parietal peritonectomy: selective parietal peritonectomy vs. complete parietal peritonectomy). During the surgical treatment, it will be taken into account that the preservation of the viscera is preferred and the invaded retroperitoneal lymph nodes will be removed. Optimal cytoreduction will be assessed by validated peritoneal staging scoring systems: CC or R-score, in which the CRS objectives are to achieve a CC-0 or CC-1 score, in which the peritoneal nodules have a diameter of less than 2.5 mm. HIPEC will be used with cisplatin and carboplatin, either alone or in combination with doxorubicin, pemetrexed, ifosfamide, and mitomycin. Mitomycin has also been used as the only chemotherapeutic agent but with a slight decrease in survival. Normothermic intraperitoneal chemotherapy with pemetrexed and other chemotherapeutic agents has also been used with a slight increase in the survival of patients with MPM.
2. Patients with well-differentiated papillary and multicystic mesothelioma will be treated with either CRS alone or HIPEC-associated CRS depending on the stage of the disease. The benefit of combining HIPEC therapy is unknown.
3. Patients with biphasic, sarcomatoid, or unresectable PMP will only be treated by systemic chemotherapy. New chemotherapeutic agents are being tested, especially for patients who have seen an increase in Ki67, seen in immunohistochemical studies.
4. The contribution of adjuvant chemotherapy to the treatment of patients with PMP is unknown. The study conducted by Sugarbaker and colleagues in 2017 [27] on long-term adjuvant combined intraperitoneal and systemic chemotherapy showed promising results. It has been shown in published studies that the response rate of malignant epithelioid mesothelioma to systemic chemotherapy is around 20%. The chemotherapeutic agents used are pemetrexed, carboplatin, cisplatin, and bevacizumab.
5. New chemotherapeutic agents such as anti-mesothelin antibody (anetumumab), anti-PDL-1 (pembrolizumab), CAR T cells, and *Listeria*-based immunotherapy can improve the survival of patients with PMP.

There are still no clear recommendations in the follow-up of patients with MPM after radical excision surgery [40]. There is a follow-up guide developed by the European Society for Medical Oncology for pleural mesothelioma, but no frequency or methods of investigation used in the postoperative period (CT, MRI, or ultrasonography) are specified. Serum follow-up markers are conventional: CA125 and mesothelin.

2.5 Conclusions

Patients with peritoneal mesothelioma, due to nonspecific symptoms, present in advanced stages of the disease. An important role in determining the histological subtype of peritoneal mesothelioma is played by immunohistochemistry. Multidisciplinary management is preferred for patients with MPM. CRS and HIPEC appear to be the most effective therapeutic modalities in the treatment of MPM. Bidirectional chemotherapy is able to increase the resectability rate in patients with diffuse MPM, initially considered unresectable. Modern therapies such as molecular therapy and immunotherapy can increase the overall survival of patients with MPM. New therapeutic approaches have improved the prognosis only for patients in the early stages of the disease.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

| | |
|-------|--|
| DMPM | diffuse malignant peritoneal mesothelioma |
| MCPM | multicystic peritoneal mesothelioma |
| BMPM | benign multicystic peritoneal mesothelioma |
| PM | peritoneal mesothelioma |
| MPM | malignant peritoneal mesothelioma |
| CRS | cytoreductive surgery |
| PSOGI | Peritoneal Surface Oncology Group International |
| HIPEC | hyperthermic intraperitoneal chemotherapy |
| PIPAC | pressurized intraperitoneal aerosol chemotherapy |
| EPIC | early postoperative intraperitoneal chemotherapy |
| NIPEC | normothermic intraperitoneal chemotherapy |
| PCI | peritoneal cancer index |
| EGFR | epidermal growth factor receptor |

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